RATIONAL FOR DEVELOPING AN ALDOSTERONE SYNTHESE INHIBITOR (ASI)

Current standard-of-care for treatment of hypertension and cardiorenal diseases includes use of a mineralocorticoid receptor antagonist (MRA) to inhibit aldosterone signaling. Despite the use of MRAs, a high unmet medical need remains. One potential reason for this is the large increase in circulating aldosterone that results from MRA treatment, leading to increased non-genomic signaling through GPR30 (GPER), which, in aging individuals, may increase renal and vascular dysfunction and remodeling.

CONCLUSIONS

- Single-ascending doses of 5–800 mg and 7-days of multiple-ascending doses of 40–360 mg of lorundrostat were well tolerated with a low incidence of adverse events.
- Mean t1/2 was 1.5–1.9 hours and mean tmax was 7.9–10.5 hours in the SAD component and t1/2 was 9.1–11.9 hours in the MAD component.
- There was a low incidence of adverse events that was not dose-dependent.
- Based on these findings, development of lorundrostat has progressed; a Phase 2 safety and dose-ranging trial in subjects with hypertension has been completed and a pivotal registration program is anticipated to begin in 2023.